CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208193Orig1s000

SUMMARY REVIEW

Summary Review

Date	9/13/2019
From	Gerald D. Podskalny, DO, MPHS Eric Bastings, MD
Subject	Summary Review
NDA/BLA # Supp #	NDA 208193
Applicant Name	Metacel Pharmaceuticals, LLC
Date of Submission	03/18/2019
PDUFA Goal Date	09/18/2019
Proprietary / Established (USAN) names	Ozobax / Baclofen
Dosage forms / strength	Oral Solution, 1 mg/mL
Proposed Indication(s)	(b) (4) spasticity resulting from 1) multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity, 2) spinal cord injuries and other spinal cord diseases.
Recommended:	**Approval**

1. Background

Metacel Pharmaceuticals, LLC (the applicant) resubmitted their 505(b)(2) New Drug Application (NDA) for Ozobax (baclofen oral solution). The resubmission addresses the deficiencies described in the second Complete Response (CR) action letter, sent on 6/25/2018. The original NDA submission was received on 3/11/2016, and the FDA's first CR action letter for the NDA issued on 1/11/2017. At the end of the first review period, FDA concluded that although the applicant had demonstrated bioequivalence to the listed drug, baclofen oral tablets, providing an adequate bridge to the FDA's finding of safety and effectiveness for Lioresal oral tablets (Novartis), product quality deficiencies precluded approval.

Additional product quality deficiencies led to a second CR letter. (b) (4) Inadequate formulation and control strategies for baclofen oral solution could not assure the identity, purity, strength and quality of the commercial drug product. In the CR letter, FDA advised the applicant to either (b) (4) or address specific product deficiencies that include:

1. (b) (4)

2. [redacted] (b) (4)

The CR letter also informed the applicant that "if the identity, assay, or related substance method has to be modified to be fully validated, drug product samples may require retesting. If there are no samples available for retesting, drug product stability studies need to be repeated, since the current data would not reliable. Therefore, the applicant should place an additional 2 batches of the drug product on stability, according to ICH Q1A (R2), and submit sufficient long-term stability data to support the proposed shelf life".

The action letter also included a related nonclinical deficiency [redacted] (b) (4)

FDA Review Team for this Application

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Cross-Discipline Team Leader	Gerald D. Podskalny
Drug Product/Labeling	Dan Berger
Manufacturing	Peter Krommenhoek
Microbiology	Gouri Chattopadhyay
Regulatory Business Process Manager	Dahlia A. Walters
Application Technical Lead	Martha Heimann
DMEPA Label and Labeling	Colleen Little
DMEPA Proprietary Name Review	Danielle Harris
Controlled Substance Staff	Edward G. Hawkins

OND- Office of New Drugs
DMEPA= Division of Medication Error Prevention and Analysis

2. Chemistry, Manufacturing and Controls/Microbiology/Device

Drug Substance
The drug substance manufacture has not changed from the initial submission. The Office of Product Quality (OPQ) concluded that the drug substance manufacture remains adequate since the first review cycle.

Drug Product
The applicant chose to address the acceptance criteria [redacted] (b) (4) (b) (4) the applicant was able to meet the acceptance criteria of not more than (NMT) [redacted] (b) (4)% after 12 months of storage. Batch analysis from two manufactured batches met the acceptance criteria [redacted] (b) (4) of NMT [redacted] (b) (4)%. Stability data included in the application was adequate to support a 12-month shelf-life under refrigerated storage conditions (2°C - 8°C). [redacted] (b) (4) (b) (4)

The applicant's risk assessment for drug product (b) (4) adequately addressed the deficiency included in the CR letter. The proposed container closure system, a light-resistant container with a child-resistant closure, is still acceptable.

Comments regarding the proposed container, and the package insert were communicated to the applicant during labeling discussions.

Manufacturing Facilities and Inspections
The Process and Facilities were both found adequate, with no deficiencies remaining after review of the first resubmission. The CMC reviewer found that minor process changes that were made to the commercial batch record are acceptable. Three new contract testing facilities were added to replace withdrawn facilities. No evaluation was necessary (b) (4) (b) (4) were approved based on their recent inspection history.

Microbiology
The applicant has changed the acceptance criteria for the Microbial Limits Testing for the DP. The acceptance criteria for the total aerobic microbial count (TAMC) and total yeast/ mold count (TYMC) were revised (b) (4) The acceptance criteria for E. coli and Burkholderia cepacia were changed (b) (4) respectively. The Microbiology reviewer concluded the changes to the acceptance criteria are acceptable. The reviewer noted that the DP (b) (4)

Recommendation from the Technical Lead
Martha Heimann, PhD, served as the CMC technical lead for review of this resubmitted application. Dr. Heimann recommends approval from a product quality perspective, with one comment to the applicant to be included in the action letter (below).

Based on the long-term stability data provided, a 12-month expiration dating period is assigned for product stored refrigerated (2°C to 8°C). We remind you that the shelf life should be calculated from the first day of manufacture.

Overall recommendation from OPQ
The Office of Product Quality (OPQ) review team recommends approval. From a quality perspective, the product is judged adequate for use provided it is stored refrigerated (2°C to 8°C). The assigned expiration dating period (expiry) for Ozobax is 12 months when stored refrigerated.

3 Safety

Postmarketing Safety
Anne C. Tobenkin, PharmD., in the Division of Pharmacovigilance I, conducted a review of the safety of baclofen. Dr. Tobenkin found 5 individual case reports of withdrawal in neonates whose mothers were treated with baclofen through the 3rd trimester, which led to a

recommendation for a Boxed Warning for neonatal abstinence syndrome (NAS). We reviewed the original FDA Adverse Event Reporting System (FAERS) case reports. A separate literature review found an additional case. Two of the 6 cases had no clear confounders and were likely cases of neonatal withdrawal. None of cases resulted in death, and none of the cases appeared to meet the criteria for NAS. A description of NAS is justified in the Warnings and Precautions section of labeling, (b) (4)

4 Labeling

Pediatrics
Baclofen oral tablets are approved for use in pediatric patients 12 years of age and older with spasticity caused by multiple sclerosis. The Pediatric Research Committee (PeRC) concurred with the division's recommendation to grant a partial waiver for children ages 0 to <12-years-old for the treatment of spasticity caused by multiple sclerosis.

Proprietary name
After review, the FDA's Division of Medication Error Prevention and Analysis notified the applicant that the proprietary name "Ozobax" is conditionally acceptable.

Controlled Substance Staff
Edward G. Hawkins, Ph.D., was the CSS reviewer for the Ozobax NDA. Dr. Hawkins concluded that baclofen is not currently controlled in the Controlled Substances Act and does not have abuse potential. In first review, CSS concluded Ozobax "will not need a section 9 of the label regarding abuse of the drug, but physical dependence should be addressed in product labeling."

Physical dependence references withdrawal symptoms that can occur after baclofen is abruptly discontinued. Withdrawal symptoms are addressed in the Warnings and Precautions section of the label which warns prescribers about abrupt withdrawal of baclofen and the potential for neonatal withdrawal.

Physician Labeling Rule
The label for Ozobax will be similar to the approved label for the listed drug. The approval of Ozobax includes label revisions needed to comply with the Physician's Labeling Rule (PLR) and sections that comply with the Pregnancy and Lactation Labeling Final Rule (PLLR).

5 Conclusions and Recommendations

As the applicant demonstrated bioequivalence between Ozobax and listed product (oral) baclofen tablets, an adequate bridge was established between the two products, which supports reliance on the FDA's finding of safety and effectiveness for baclofen tablets. Product Quality deficiencies described in the last Complete Response letter have been resolved. Therefore, we will issue an approval letter for this application.

Comments to be conveyed to the applicant in the regulatory action letter

Product Quality

Based on the long-term stability data provided, a 12-month expiration dating period is assigned for product stored refrigerated (2°C to 8°C). We remind you that the shelf life should be calculated from the first day of manufacture.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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09/13/2019 09:36:00 AM

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09/13/2019 10:28:07 AM